



Canadian Agency for
Drugs and Technologies
in Health

RAPID RESPONSE REPORT: SUMMARY WITH CRITICAL APPRAISAL



TITLE: Endovascular Thermal Ablation Technologies for Treatment of Varicose Veins: A Review of Clinical Effectiveness, Safety, Cost-Effectiveness and Guidelines – An Update

DATE: 19 August 2014

CONTEXT AND POLICY ISSUES

Varicose veins are enlarged tortuous superficial veins at least 3mm in diameter that usually affect the great (GSV) and small (SSV) saphenous veins in the lower limbs.^{1,2} Varicose veins are caused by decreased elasticity of the vein wall and poorly functioning valves within the vein, resulting in blood pooling in the veins and vein enlargement.^{2,3} The symptoms of varicose veins can range in severity from occasional discomfort to severe ulceration of the skin.^{1,2} Approximately 10 to 40% of Western populations have varicose veins, and varicosities can cause considerable disability, resulting in decreased quality of life and loss of work days.^{1,2} If left untreated, varicose veins can progress to chronic venous insufficiency, which increases the likelihood of tissue damage and development of venous stasis ulcers.¹

Surgery, including saphenous vein ligation and stripping, has been standard therapy for the treatment of varicose veins.^{4,5} Surgery, however, is invasive and may be associated with a greater incidence of complications and slower recovery relative to newer treatments such as endovascular thermal ablation (EVTA).⁶ Sclerotherapy is also a common therapy for smaller varices (< 4mm) in patients with less severe disease, but multiple treatments are often required.^{7,8} EVTA, which includes laser (EVLT) and radiofrequency ablation (RFA), are therapies that are less invasive than surgery, and preliminary data suggest that EVTA is associated with similar treatment success rates with reduced recovery time and complications relative to surgery.⁶ EVTA requires specialized equipment and training, however, and it is unclear whether long-term clinical effectiveness, safety, and cost-effectiveness is improved with EVTA therapies relative to traditional therapies including surgery and sclerotherapy. In addition, it is unclear whether there are differences in terms of effectiveness and complications between EVLT and RFA.

The purpose of this review is to provide an update of a Rapid Response report produced by CADTH in 2011.⁹ It compares the available evidence for the treatment of uncomplicated varicose veins, with a focus on endovascular thermal ablation compared with surgery or

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sclerotherapy, and EVLT compared with RFA, in terms of clinical effectiveness, safety, cost-effectiveness, and evidence-based guidelines.

RESEARCH QUESTIONS

1. What is the comparative clinical effectiveness of endovascular thermal ablation of varicose vein technologies versus standard treatment for varicose veins?
2. What is the comparative safety of endovascular thermal ablation of varicose vein technologies versus standard treatment for varicose veins?
3. What is the comparative cost-effectiveness of endovascular thermal ablation of varicose vein technologies versus standard treatment for varicose veins?
4. What is the comparative clinical effectiveness of endovascular laser therapy versus radio frequency ablation for the treatment of varicose veins?
5. What is the comparative safety of endovascular laser therapy versus radio frequency ablation for the treatment of varicose veins?
6. What is the comparative cost-effectiveness of endovascular laser therapy versus radio frequency ablation for the treatment of varicose veins?
7. What are the evidence-based guidelines and recommendations for endovascular thermal ablation of varicose vein technologies for treatment of varicose veins?

KEY FINDINGS

Non-invasive procedures, like EVLT, RFA and ultrasound-guided foam sclerotherapy (UGFS), are not inferior to surgery in terms of clinical effectiveness with potential benefits in terms of time to return to normal activity, complications and cost-effectiveness. Little or no clinical effectiveness or safety differences between non-invasive procedures have been observed. Cost is more likely to determine cost-effectiveness between them.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014 July, Issue 7), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic studies, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2011 and July 14, 2014. A database search update was conducted on August 4, 2014.

Selection Criteria and Methods

One reviewer screened the literature search results to identify relevant publications, including health technology assessments (HTAs), systematic reviews (SRs) and meta-analyses (MA), randomized controlled trials (RCTs), non-randomized studies, economic evaluations, and clinical practice guidelines (CPGs) based on publication title and abstract. Full-text articles were considered for inclusion based on the selection criteria listed in Table 1.

Population	Patients with varicose veins Subpopulation: working age patients with varicose veins
Intervention	Endovascular thermal ablation (EVTA) – including endovascular laser therapy (EVL) and radio frequency ablation (RFA)
Comparator	EVL and RFA versus standard treatment (surgery and sclerotherapy); EVL versus RFA
Outcomes	Clinical benefits, clinical harms, cost-effectiveness, guidelines and recommendations
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, economic evaluations, clinical practice guidelines

Exclusion Criteria

Articles were excluded if there were duplicates of a selected study, if they were already included in a SR or HTA, if they were included in the 2011 Rapid Review,⁹ if a more recent update was available, if they were non-systematic reviews, or if they did not meet the inclusion criteria. Given the availability of higher quality evidence, non-randomized studies were excluded during full-text screening.

Critical Appraisal of Individual Studies

Health technology assessments and systematic reviews were appraised using the AMSTAR (A Measurement Tool to Assess Systematic Reviews) checklist.¹⁰ Items included in the AMSTAR checklist include a priori design of the review, eligibility criteria, information sources searched, study selection, data items and methods of data extraction, quality of studies, interpretation of the results, publication bias, and sources of funding.¹⁰

Randomized controlled trials were appraised using the Downs and Black checklist.¹¹ Items evaluated included clear study objectives, clear study inclusion and exclusion criteria, clear description of potential confounders, description of losses to follow up, blinding, appropriate statistical tests used., accuracy of the outcome measures, and whether power was sufficient to detect a difference if one existed.¹¹ A numeric score was not calculated. Strengths and limitations were reviewed for included studies.

Cost-effectiveness studies were appraised using Drummonds checklist.¹² Items evaluated included whether the question was well-defined and answerable, whether evidence exists that demonstrates the program’s effectiveness, whether all important outcomes and costs for each alternative were considered, were costs measured appropriately, was discounting used to

account for costs at different times, and can the results be applied to the local population.¹² An overall numeric score was not calculated. Strengths and limitations were reviewed for included studies.

Guidelines were appraised using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument.¹³ The items included in the AGREE instrument are scope and purpose of the guideline, stakeholder involvement, rigour of development, clarity and presentation, applicability, and editorial independence.¹³ Similar to the critical appraisal of RCTs, an overall numeric score was not calculated; instead, strengths and limitations were reviewed narratively for available guidelines.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 153 citations were identified in the literature search. After screening of titles and abstracts, 41 articles were selected for full-text screening. After further exclusion of non-randomized studies and inclusion of citations retrieved from grey literature, hand search, and literature search updates, 11 citations were included in this report. Of the studies included, one is a HTA,¹⁴ two are SRs,^{15,16} four are RCTs,¹⁷⁻²⁰ three are clinical practice guidelines²¹⁻²³ and one is a recommendation report.²⁴ Appendix 1 describes the PRISMA flowchart of the included studies in this report.

The summary of study characteristics table is provided in Appendix 2, the results of the critical appraisal are in Appendix 3, and the main study findings and author conclusions are provided in Appendix 4.

Summary of Study Characteristics

Comparative clinical effectiveness and safety of endovascular thermal ablation technologies versus standard treatment and other endovascular thermal ablation technologies

A total of 7 studies were identified that compared clinical effectiveness of EVTA with standard therapy including surgery or sclerotherapy. Of these publications, one was a health technology assessment,¹⁴ two were systematic reviews,^{15,16} four were randomized controlled trials,¹⁷⁻²⁰

The safety of EVTA was compared with standard therapy in six studies. Of these publications, one was a health technology assessment,¹⁴ two were systematic reviews,^{15,16} three were randomized controlled trials.¹⁸⁻²⁰

Clinical effectiveness of EVLT was compared with RFA in a health technology assessment report.¹⁴

One health technology assessment report¹⁴ compared the safety of EVLT and RFA.

Country of Origin

RCTs originated from United Kingdom (UK),^{17,20} The Netherlands¹⁸ and Iran.¹⁹ The health technology assessment was from UK,¹⁴ systematic reviews were from UK¹⁵ and The Netherlands.¹⁶

Population

The mean or median age of patients in the included studies ranged from 33 to 56 years,^{14,15,18} and the majority of the study populations were female (50% to 95%).^{14,15} Most studies included patients with varicose veins associated with great saphenous vein and saphenofemoral joint insufficiency and reflux.^{15,17-19} Two studies only included patients with small saphenous vein insufficiency.^{16,20} An HTA included procedures for both great and small saphenous veins.¹⁴ The sample sizes of the randomized controlled trials ranged from 65¹⁹ to 223.¹⁸ Randomized controlled trials included in the SRs or HTA have sampled from 28 to 710 patients with a total maximum of 3,873 patients.¹⁴

Intervention

EVLT wavelength varied between studies from 810 nm to 1470 nm.¹⁴ The surgical procedure used in the studies was high ligation and stripping most of the time, while some studies could include high ligation only^{14,16} or stripping only.¹⁶ Studies that evaluated RFA included different RFA catheters. The VNUS Closure, the VNUS ClosureFast and the Olympus RFiTT systems were those used most often.¹⁴

Years of publication

The years of publication ranged from 2011 to 2014.

Comparative cost-effectiveness of endovascular thermal ablation technologies versus standard treatment and other endovascular thermal ablation technologies

Three publications comparing cost-effectiveness of interventions have been reviewed including a HTA,¹⁴ a systematic review¹⁶ and a clinical practice guideline.²²

The HTA was from the National Health Service of United Kingdom.¹⁴ A systematic review of all studies comparing non-invasive varicose veins treatments has been performed up to September 2012. Four economic analyses, two analyses conducted alongside RCTs and two economic models, were included for cost-effectiveness assessment.¹⁴ An economic model simulating the experience of patients undergoing treatment has been developed as a discrete event simulation.¹⁴ Included treatments were surgery, UGFS, EVLT and RFA. The baseline model had a time horizon of 10 years. The considered treatments are for symptom relief and were assumed not to affect mortality. The analysis was from the NHS perspective. Initial procedure costs, additional treatment (top-up sclerotherapy) costs, and retreatment (if failure) costs were taken into account. All costs and benefits were discounted at a rate of 3.5%.¹⁴

The systematic review performed by Tellings et al. in The Netherlands aimed at retrieving studies on cost-effectiveness and time-effectiveness of treatment of SSV varicose veins.¹⁶ Three reports, that had discussions on cost-time effectiveness of treatments, were included.¹⁶

The clinical practice guideline released by the National Institute for Health and Care Excellence (NICE) in United Kingdom had a systematic review of the economic evidence on varicose veins management.²² Full economic analyses, such as cost-effectiveness, cost-utility, cost-benefit and cost-consequence studies, were included. Economic evidence was presented for each review question. The authors also developed an economic Markov model from a payer (NHS and social services) perspective. A cost-utility analysis based on a network meta-analysis of clinical recurrence was conducted. Treatment of GSV incompetence included surgery, EVTA, UGFS and conservative care. Surgery was considered as a day case procedure under general anaesthetic, while EVTA and UGFS were carried out as outpatient procedures under local anaesthetic. Statistical models for fixed and random effects were used. Initial procedure costs, additional treatment (top-up sclerotherapy) costs, second treatment (if failure) costs, and costs associated with physical symptoms (e.g. symptom management costs) were taken into account. When no economic analysis was found to assign as cost, relevant NHS costs were used. A 3.5% discount for costs and utility was used. The time horizon was 5 years.²²

Evidence-based guidelines and recommendations for endovascular thermal ablation technologies for treatment of varicose veins

Country of origin

The clinical practice guidelines were from NICE in the UK,²² from the American College of Radiology (ACR) in the USA,²¹ from an international group overseen by the International Union of Phlebology.²³ The recommendation report was from the Ontario Health Technology Assessment Committee (OHTAC) of Canada.⁹

Population

The guidelines and recommendations were meant for a population of adult patients with GSV varicose veins and reflux.^{9,21-23} One guideline also gave specific recommendations for pregnant women with varicose veins.²²

Interventions

Intervention reviewed included surgery (high ligation and stripping),^{21,22} EVLT,²¹⁻²³ RFA,²¹⁻²³ sclerotherapy^{21,22} and compression therapy.^{21,22}

Years of publication

The studies included were published from 1990 to 2014,²³ with a majority between 2000 and 2012.

Grading of recommendation

The guidelines from ACR used a recommendation scale from 1 to 9 where 1, 2, 3 are “usually not appropriate”, 4, 5, 6 “may be appropriate” and 7, 8, 9 are “usually appropriate” treatments or procedures.²¹ Pavlovic et al. graded their recommendations according to the American College of Chest Physicians Task Force where 1 and 2 are strong and weak recommendations, respectively; and A, B, C are high, moderate and low (or very low) quality evidence, respectively.²³

Summary of Critical Appraisal

Comparative clinical effectiveness and safety of endovascular thermal ablation technologies versus standard treatment and other endovascular thermal ablation technologies

The health technology assessment from NHS had a clear description of design, comprehensive literature search, duplicate data extraction and critical appraisal.¹⁴ The overall quality of included studies was average. Selected studies were deemed at high risk of detection bias since most of them were not blinded. Surgeon experience, randomization method, concealment of treatment allocation, non-comparability of groups at baseline and non-identical care programs were also an issue in some studies. Finally, the NHS report did not assess publication bias or conflict of interest in the studies.¹⁴

The strengths of the systematic reviews included descriptions of included studies and their characteristics, and assessment of study homogeneity.^{15,16} Comprehensive literature searches, search for grey literature, study selection, individual quality of included studies, and a list of excluded studies have been clearly described and conflicts of interest have been addressed in only one¹⁵ of the two SRs. Regarding to individual quality assessment, Nesbitt et al. have raised the non-blinding issue in all studies and the randomization method, in some studies, as potential biases.¹⁵ In terms of limitations, Tellings et al. have not mentioned the years of literature search or a pre-determined protocol for their review and publication bias has not been assessed.¹⁶

Although one study have enrolled patients in a lower age range¹⁹ and GSV insufficiency represent a minority of cases,²⁰ included RCTs have used patient populations and interventions that were representative of real practice. All RCTs¹⁷⁻²⁰ clearly described patient subjects, randomization methods, outcomes, interventions, findings and gave actual *P* values for main outcomes, with the exception of Mozafar et al.¹⁹ which did not disclose their randomization procedure and did not perform a statistical test on their primary outcome. All RCTs have used duplex ultrasonography, considered as the gold standard technique, to diagnose reflux at baseline and measure recurrence after intervention.¹⁷⁻²⁰ All RCTs,^{17,18,20} but one,¹⁹ have performed a sample size calculation for their main outcomes. However, all RCTs were open-labeled. Also, one study had lower percentage of enrolment in the surgery group compared with other groups.¹⁸ Other concerns were: source population not clearly stated,¹⁷ percentage of patients from each hospital not disclosed,¹⁸ losses to follow-up not described,^{17,20} and baseline confounders not taken into account.¹⁷

Comparative cost-effectiveness of endovascular thermal ablation technologies versus standard treatment and other endovascular thermal ablation technologies

According to the authors of the HTA, the two economic studies reviewed by NHS both had seriously flawed economic analyses, including incorrect calculation of ICERs and incorrect calculation of cost-effectiveness, although data allowed proper recalculation.¹⁴ The two included modelling studies were also of poor quality, with very short follow up (2 weeks), overestimation of pain disutility, high uncertainty of parameters, absence of sensitivity tests or high sensitivity of the results to changes in model inputs.¹⁴ The model developed by NHS was derived from a systematic review and meta-analysis using a mixed-treatment comparison. The authors had explicit research questions and description of treatment options. They included direct costs with their references and sensitivity analyses were performed. The model was limited by the quality

of treatment failure data and the limited evidence of differences between treatments in post-procedure utility. Generalizability of costs in the UK could be problematic in Canada.

As previously described, the systematic review made by Tellings et al. was of poor overall quality.¹⁶ Years of literature search, data extraction, included studies, excluded studies and quality appraisal were poorly or not described. Moreover, studies included for assessment of cost-time effectiveness evidence were of poor quality. The three included reports were not economic analyses, but non-randomized studies that discussed the cost-time effectiveness of the compared treatments.¹⁶

The systematic review and the development of guidelines by NICE was deemed of very good quality in accordance to AGREE II criteria.²² For the economic evaluation, the authors had explicit research questions and description of treatment options. They included direct costs with their references and sensitivity analyses were performed. Heterogeneity and inconsistency of the network meta-analysis were investigated. Generalizability of costs in UK could be problematic in Canada. EVLT and RFA have been assessed together as EVTA procedures, so cost-effectiveness differences between these two cannot be estimated. Also, the model assumed that all patients are eligible for all interventions which may not be the case in practice.²²

Evidence-based guidelines and recommendations for endovascular thermal ablation technologies for treatment of varicose veins

As previously described, NICE has performed a rigorous and comprehensive systematic review on varicose vein management and has provided a clear description of scope, purpose, methodology, stakeholder involvement, evidences, safety issues, critical appraisal, recommendations, conflicts of interest and tools for implementation.²² The only negative observation, apart from its applicability to the Canadian health system, was the limited information regarding external review process.²²

The clinical practice guidelines published by Pavlovic et al. had well described recommendations graded depending on available evidence, where studies were cited.²³ The patient perspective has been considered and authors declared no conflict of interest. However, methodology, health questions covered, composition of the development group and target users were poorly described. Assessment of bias in the covered literature, applicability, external review or updating process have not been mentioned.²³

The clinical practice guidelines of the American College of Radiology (ACR) clearly presented evidence and their limitations.²¹ Key recommendations and treatment options were easily identifiable. Nevertheless, this CPG had serious limitations in terms of comprehensive description of objectives, research questions, development group, reviewing process, applicability and conflicts of interest. The methodology has been described in a different document and was general to every ACR guidelines, thus rigor of development could not be appraised.²¹

Summary of Findings

Comparative clinical effectiveness and safety of endovascular thermal ablation technologies versus standard treatment and other endovascular thermal ablation technologies

Clinical outcomes – EVTA compared with surgery or sclerotherapy

Most studies found that clinical recurrence, defined by incomplete occlusion, symptomatic recurrence or recurrence of reflux, was no different^{14,15,17-19} in people who received surgery compared to EVTA. On the other hand, some studies favored EVTA in short term (after 6 weeks, 96.2% vs 71.7%, $P < 0.001$),²⁰ but not in longer term (after 1 year, 16.9% vs 9.4%, $P = 0.390$),²⁰ and EVLT+UGFS (94.9% vs 47.8%, $P < 0.05$)¹⁶ over surgery. Neovascularisation (Odds Ratio [OR] 0.05, 95% confidence interval [CI] 0.01 to 0.22, $P < 0.0001$) and technical failure (OR 0.29, 95% CI 0.14 to 0.60, $P = 0.0009$) were improved with EVLT compared with surgery.¹⁵ In terms of return to normal activity, Samuel et al. favored EVLT over surgery ($P < 0.001$).²⁰ Moreover, Carroll et al. reviewed a majority of studies (5/7) that reported significantly quicker return to normal activity after RFA or UGFS compared with surgery.¹⁴ Pain score comparison favored RFA over surgery (median: -1.26 (95% credible interval [CrI], -1.95 to -0.61)^{14,15}, while Nesbitt et al. concluded that results comparing EVLT are conflicting.¹⁵ Improvement of severity scores (Venous clinical severity score [VCSS]), Clinical status-etiology-anatomy-pathophysiology [CEAP], saphenous treatment score [STS]) were found in one study when comparing UGFS vs stripping (UGFS favored -1.63 [95% CI -2.90 to -0.42])¹⁴ but most of the studies found no difference between groups.^{15,17-20} Quality of life^{15,17,18,20} or patient satisfaction¹⁹ were similar after each intervention, except in one study where Aberdeen varicose vein questionnaire (AVVQ) score was improved after EVLT vs surgery (after 12 months, $P < 0.019$, after 18 months, $P < 0.008$).¹⁹

Clinical outcomes – EVLT compared with RFA

One study comparing EVLT with RFA found no significant clinical difference between these two interventions.²⁰

Safety – EVLT compared with standard therapy and RFA

Serious complications, including deep-vein thrombosis, sural nerve damage, severe wound problems or pulmonary embolism, were rare.^{14-16,18,20} Adverse events such as bruising, hematoma, paresthesia, infection, and phlebitis were more common.^{14-16,20} Wound infection and sensory problems risks were reported to be lower²⁰ or equal¹⁹ after EVLT compared with surgery. However, a systematic review reported similar distribution of complications when comparing UGFS, EVLT, RFA and surgery.¹⁵

Comparative cost-effectiveness of endovascular thermal ablation technologies versus standard treatment and other endovascular thermal ablation technologies

Overall, the economic analyses included by the NHS review were of limited scope and quality.¹⁴ However, they do demonstrate that differences between treatments are small and sensitive to assumptions. The cost-effectiveness of the different procedures is likely to be uncertain and vary by local costs. Differences between treatments were negligible in terms of clinical outcomes (QALYs), so the treatment with the lowest cost appeared to be most cost-effective.¹⁴ The modeling analysis showed that RFA is the most expensive procedure (£2,635) and UGFS is the least (£634). QALY differences between surgery, EVLT and RFA were negligible. Neither EVLT or RFA was considered cost-effective compared with surgery. All parameters of this result, including time, were robust to sensitivity tests. UGFS is marginally more effective than

surgery. At thresholds between £20,000 and £50,000, UGFS is the most cost-effective treatment, with a <10% probability of error. This result was sensitive to time horizon.¹⁴

Three studies were retrieved by Tellings et al. for their cost-effectiveness content.¹⁶ One stated that the choice for either EVLT or RFA depends on the cost of equipment, disposables, and procedure time. The two other articles stated that the differences between surgery and UGFS are self-evident regarding costs. The authors of the review did not provide more details on cost-effectiveness of treatment of SSV reflux.¹⁶

Based on the economic model analysis of NICE, surgery was the most expensive treatment (£1,222).²² UGFS was considered the least costly treatment (£718) with a probability of 23% of being the most cost-effective option. EVTA was more costly (£869) than UGFS but had an increased utility with an ICER of £3,161/QALY. EVTA had a 71% probability of being the most cost-effective treatment. These results were robust to changes in model parameters.²²

Evidence-based guidelines and recommendations for endovascular thermal ablation technologies for treatment of varicose veins

NICE recommended the following treatment hierarchy for treatment of varicose veins: RFA > EVLT > UGFS > surgery.²² Pregnant women were recommended to receive compression hosiery instead of interventional treatment.²²

Pavlovic et al.²³ have provided the following recommendations: Many veins (All Grade 1, Evidence Level A to C) are indicated for EVTA, including GSV, SSV and accessory saphenous vein. EVTA can be carried out on more than two veins during a single procedure. RFA has some specific requirements for vein length, while EVLT does not. EVTA requires that the vein be free of obstruction to enable catheter advancement. Calculations are recommended for determining the appropriate energy of treatment with EVTA (Grade 1A). Major complications to consider with EVTA are deep-vein thrombosis and pulmonary embolism in less than 2% of cases (Grade 1C). Minor complications are pain, bruising, erythema, hematoma, hyperpigmentation, paresthesia (Grade 1C). Adjunctive phlebectomy or UGFS may be performed.²³

The American College of Radiology deemed EVLT or RFA as “usually appropriate” (score of 7 to 9 on a scale of 1 to 9) for treatment of varicose veins in five specific clinical situations.²¹ These situations included symptomatic or asymptomatic GSV, SSV or bilateral insufficiency.²¹ Pregnancy and chronic left femoral venous thrombosis with GSV insufficiency were the only two scenarios where EVTA procedures were not recommended. In each of the seven situations reviewed, injection sclerotherapy and surgery were not considered as “usually appropriate”.²¹

Based on their previous HTAs, the Ontario Health Technology Assessment Committee stated that EVLT and RFA are less invasive, yet safe and cost-effective, alternatives to surgery for treatment of symptomatic varicose veins with saphenous reflux.²⁴ They recommended that EVTA should be made available when bleeding, thrombophlebitis, or venous ulcers are observed. Chronic venous reflux should also be included if the intervention is based on severity scale like VCSS and not on cosmetic reasons.²⁴

Limitations

As comparators have significant differences in terms of procedure and are difficult to hide, patients and investigators could not be blinded in the studies.¹⁴⁻²⁰ Hence, some studies had a decreased percentage of enrolment in the surgery group compared with non-invasive intervention groups that may reflect a selection bias.¹⁸ Furthermore, variations in the reporting results limited meaningful meta-analyses for the majority of outcome measures.¹⁵ The most common outcome, that is clinical recurrence, is often defined as an incomplete occlusion of the GSV. As shown by Lattimer et al.,¹⁸ it is not clear whether that outcome correlates with reflux abolishment or with symptomatic recurrence that may represent more clinically relevant end points.

The cost-effectiveness of varicose vein treatments varies with local initial costs and settings which may differ in a Canadian context.¹⁴ There is uncertainty in cost differentials between treatments as they may vary over time.¹⁴ There are some discrepancies about the most cost-effective treatment (UGFS or EVTA procedures) in two rigorous studies from UK.^{14,22}

For the aforementioned reasons, including methodology concerns, clinical practice guidelines from Pavlovic et al.²³ and from ACR²¹ were of inferior overall quality compared with the report from NICE.²² It has also been mentioned that quality of clinical evidence from RCTs was low because of lack of allocation concealment.²² A high level of imprecision has also been observed for most outcomes.²²

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Most of the studies included in this review compared non-invasive procedures with surgery. Few reports have addressed the comparison between EVLT and RFA. However, those were reports of high quality level like HTA, SRs and exhaustive CPGs. But given the nature of the interventions, RCTs included in the present review and other reviews were open-labeled studies, limiting the strength of the available evidence.

Most of the available evidence showed similar or slight differences in clinical effectiveness between EVLT, RFA, UGFS and surgery although some studies found effectiveness benefits with non-invasive procedures. Surgery was associated with more pain compared to RFA and longer convalescence, higher risks of infection, or sensory problems when compared with non-invasive treatments. The decrease of clinical severity and the increase of quality of life observed after treatment were comparable with all the reviewed procedures. Patient satisfaction was also similar.

Cost-effectiveness advantages over surgery had been attributed to EVTA and UGFS, respectively, in two different good quality reports from UK. However, discrepancies between these two studies in terms of cost-effectiveness at a threshold of £20,000 were observed for EVTA procedures. Therefore, cost-effectiveness of EVTA over surgery is not clear. Taken together, these economic studies highlight the cost-effectiveness sensitivity to local costs input and assumptions as well as their questionable applicability to the Canadian context.

Our findings are in line with most of those previously reported by CADTH.⁹ In the previous report, EVTA was found as effective as surgery with some potential benefits. However, superiority of EVTA over foam sclerotherapy could not be concluded from the latest review as

conflicting results were observed. The evidence reviewed also had the same limitations than previously with non-blinded studies and very few studies comparing EVLT and RFA.

In conclusion, non-invasive procedures, like EVLT, RFA and UGFS, are not inferior to surgery with potential benefits in terms of pain, time to return to normal activity, complications and cost-effectiveness. Hence, our findings are in accordance with Ontario Health Technology Advisory Committee recommending implementation with guidance on their clinical eligibility. Little or no clinical effectiveness or safety differences between non-invasive procedures have been observed. Cost is more likely to determine cost-effectiveness between them.

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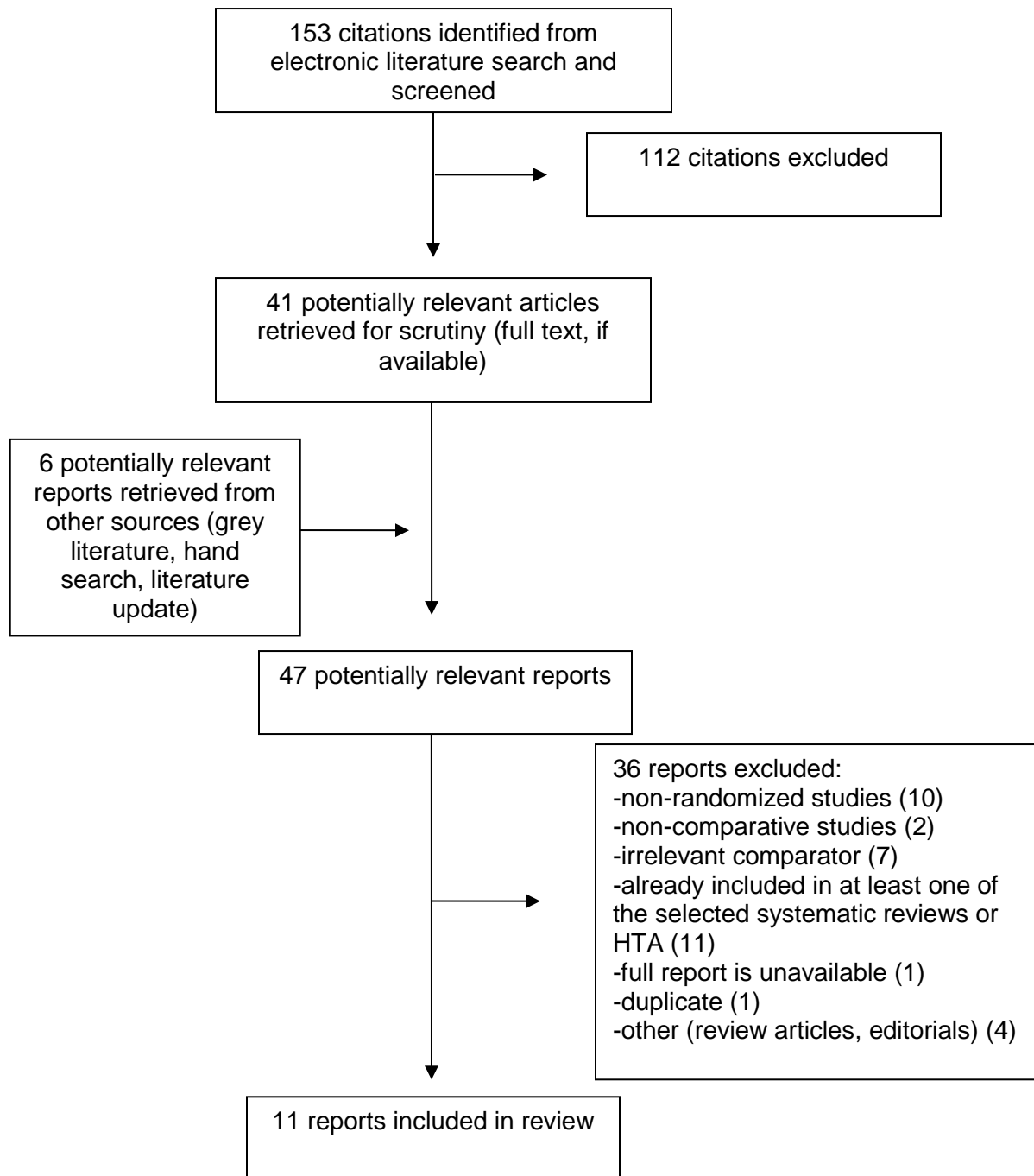
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APPENDIX 1: Selection of Included Studies



APPENDIX 2: Summary of Included Studies

First Author, Publication Year, Country	Study design, Length of Follow-up	Patients Characteristics, Sample Size (n)	Intervention	Comparator(s)	Outcomes
Health Technology Assessment					
NHS (Carroll <i>et al.</i>), 2013, ¹⁴ United Kingdom	HTA, Clinical: included literature up to July 2011. Economic literature: included CEA, CUA, CBA, up to Sept 2012, an economic model has been developed.	Included English language RCTs, patients 16 years of age and older. No minimal duration of follow-up.	EVLT, RFA, foam sclerotherapy, transilluminated-powered phlebectomy	Any form of varicose veins management	<p>Clinical:</p> <ul style="list-style-type: none"> ▪ Failure of the procedure ▪ Recurrence ▪ Clinical symptoms measured by the VCSS ▪ Pain ▪ Time to return to work or normal activity <p>Safety:</p> <ul style="list-style-type: none"> ▪ Post-operative complications (adverse events) <p>Cost-effectiveness</p>
Systematic Reviews					
Nesbitt, 2014, ¹⁵ United Kingdom	SR/MA of RCTs on the treatment of GSV varices. Update of 2011 Cochrane review, included literature up to January 2014.	13 studies, 3081 patients. 3 studies compared UGFS vs surgery, 8 EVLT vs surgery, 5 RFA vs surgery. Sample size range from 28 to 390 patients. Mean age range: 33 to 56 years. Female % range: 50 to 93.	EVLT, RFA, UGFS	Surgery (HLS)	<ul style="list-style-type: none"> ▪ Recurrent varicosities (clinical and symptomatic) ▪ Recanalisation ▪ Neovascularisation ▪ Technical failure ▪ QoL scores ▪ Complications
Tellings, 2011, ¹⁶ Netherlands	SR of all studies on the treatment of SSV insufficiency	17 reports: 5 surgery, 10 EVLT, 2 ultrasound-guided foam sclerotherapy	All treatments	All treatments	<ul style="list-style-type: none"> ▪ Clinical effectiveness ▪ Patient satisfaction ▪ Complications ▪ Cost-time

					effectiveness
RCTs					
Mozafar, 2014, ¹⁹ Iran	RCT, open-label, Length of follow-up: up to 18 months	EVLT n = 30 patients, 73% females Surgery n = 35 patients, 71 % females Mean age: 39 years, patients had GSV or saphenofemoral joint (SFJ) insufficiency with reflux and symptoms or chronic venous insufficiency	EVLT	Surgery (High ligation of saphenous vein)	<ul style="list-style-type: none"> ▪ Clinical recurrence ▪ Severity (CEAP staging, VCSS score) ▪ Patient satisfaction
Biemans, 2013, ¹⁸ Netherlands	RCT, open-label, Length of follow-up: 1 year	EVLT (n = 78), 69% women, mean age : 49. UGFS (n = 77), 68% women, mean age: 56. HLS (n = 68), 68% women, mean age: 52. Patients had primary symptomatic GSV and SFJ	EVLT, ultrasound-guided foam sclerotherapy	Surgery (high ligation and stripping)	<ul style="list-style-type: none"> ▪ Anatomic success ▪ Complications ▪ Improvement of CEAP staging ▪ Improvement of QoL
Lattimer, 2013, ¹⁷ United Kingdom	RCT, open-label, Length of follow-up: 15 months (preliminary results)	EVLT + phlebectomy (n = 44), mean age : 47, 61% women. UGFS (n = 46), mean age: 50, 54% women. Patients had GSV venous reflux.	EVLT + phlebectomy	Ultrasound-guided foam sclerotherapy	<ul style="list-style-type: none"> ▪ GSV occlusion ▪ Severity (VCSS, STS) ▪ QoL (AVVQ)
Samuel, 2013, ²⁰ United Kingdom	RCT, open-label, Length of follow-up: up to 1 year	EVLT (n =53), 64% women. Surgery (n = 53) 76% women. Mean age: 48 Patients had unilateral	EVLT	Surgery (ligation and stripping)	<ul style="list-style-type: none"> ▪ Abolition of SSV reflux ▪ Pain scores ▪ Recovery time ▪ Complication rates ▪ Severity (VCSS)

		primary saphenopopliteal junction incompetence and SSV reflux			<ul style="list-style-type: none"> QoL
Clinical Practice Guidelines					
Pavlovic, 2014, ²³ International	CPG	Guideline drafted during consensus conference in collaboration with the International Union of Phlebology, based on a systematic review.	EVTA procedures	EVTA procedures	<ul style="list-style-type: none"> Efficacy Safety Tolerability Patient satisfaction/preference Cosmetic outcome
NICE clinical guideline 168 [CG168]. Varicose veins in the legs: the diagnosis and management of varicose veins. July 2013, ²² United Kingdom	CPG	Guideline development group has made a systematic review.	All treatments evaluated	All treatments evaluated	<ul style="list-style-type: none"> Patient management (referral, treatment) Efficacy of conservative vs interventional treatments Cost-effectiveness Safety Provides information for patients and carers
Rochon, 2012, ²¹ USA (ACR Appropriateness Criteria® radiologic management of lower-extremity venous insufficiency)	CPG	Based on a literature review, but not explicitly described.	EVLT, RFA, surgical vein stripping, injection sclerotherapy, compression therapy	Same as interventions	<ul style="list-style-type: none"> Efficacy Complications

Recommendations					
Ontario Health Advisory Committee, 2013, ²⁴ Canada	Recommendations	Based on 2 HTAs from Health Quality Ontario (2011 and 2010).	EVLT, RFA	EVLT, RFA, surgery (vein ligation + stripping)	<ul style="list-style-type: none"> ▪ Effectiveness ▪ Durability ▪ Health-related quality of life ▪ Patient satisfaction ▪ Safety

ACR = American College of Radiology; AVVQ = Aberdeen varicose veins questionnaire; CBA = cost-benefits analysis; CEA = cost-effectiveness analysis; CEAP = Clinical-Etiology-Anatomy-Pathophysiology; CPG = clinical practice guidelines; CUA = cost-utility analysis; EVLT = endovenous laser therapy; EVTA = endovenous thermal ablation; GSV = great saphenous vein; HLS = high ligation and stripping; HTA = health technology assessment; MA = meta-analysis; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; QoL = quality of life; RCT = randomized controlled trial; RFA = radio frequency ablation; SFJ = saphenofemoral junction; SR = systematic review; SSV = small saphenous vein; STS = saphenous treatment score; UGFS = ultrasound-guided foam sclerotherapy; USA = United States of America; VCSS = Vascular Clinical Severity Score; w/o = without.

APPENDIX 3: Critical Appraisal of Included Studies

First Author, Publication Year, Country	Strengths	Limitations
Health Technology Assessments		
<p>NHS (Carroll <i>et al.</i>), 2013,¹⁴ United Kingdom</p>	<ul style="list-style-type: none"> • Review (clinical and economic): Clear description of a priori design, literature search, duplicate study selection, selection criteria, list of all studies with their characteristics and appraisal. Conclusions reflected the quality of studies. Homogeneity of included studies has been addressed. • Economic model: Study had a well defined question, description of the competing treatments and established effectiveness of the therapies. Perspective, time horizon, discounting were stated. Costs with their references were disclosed and appropriate. Sensitivity analyses were performed and conclusions were adequate. 	<ul style="list-style-type: none"> • Review (clinical and economic): Publication bias has not been assessed. No declaration of conflict of interest or sources of funding. • Economic model: Applicability of costs from United Kingdom to Canada remains uncertain.
SRs		
<p>Nesbitt, 2014,¹⁵ United Kingdom</p>	<p>A priori-designed SR with MAs.</p> <p>Clear description of literature search, duplicate study selection, list of included & excluded studies, their characteristics, their critical appraisal.</p> <p>Homogeneity and possibility of publication bias or conflict of interest have been assessed.</p>	
<p>Tellings, 2011,¹⁶ Netherlands</p>	<p>Clear description of included studies and its characteristics.</p> <p>Homogeneity has been assessed.</p>	<p>A review protocol has not been mentioned.</p> <p>Years of literature search and</p>

		<p>duplicate study selection was not mentioned. Inclusion of grey literature is unclear.</p> <p>List of excluded studies is not shown.</p> <p>Individual quality of studies was not described.</p> <p>Publication bias was not assessed.</p> <p>Conflicts of interest were not assessed.</p> <p>Studies included for cost-time effectiveness assessment were of poor quality.</p>
RCTs		
Mozafar, 2014, ¹⁹ Iran	<p>Inclusion and exclusion criteria, subject characteristics and interventions were described.</p> <p>Measurement of reflux by duplex ultrasound deemed to be accurate.</p> <p>No loss to follow up.</p>	<p>Study subjects and people measuring study outcomes were not blinded.</p> <p>No statistical test for main outcome.</p> <p>No power calculation, very small samples size.</p> <p>% of enrolment not mentioned.</p> <p>No description of randomization procedures or whether it was concealed until recruitment.</p>
Biemans, 2013, ¹⁸ Netherlands	<p>Clear description of subjects, adequate randomization, outcomes, interventions, findings, actual <i>P</i> values.</p> <p>Measurement of reflux by duplex ultrasound deemed to be accurate.</p> <p>Sample size calculation.</p> <p>Physicians had more than 5 years of experience with the treatment.</p>	<p>Study subjects and people measuring study outcomes were not blinded.</p> <p>Number of patients from each hospital in each group is not mentioned, although subgroup analysis didn't show any difference between the two centers.</p> <p>% of enrolment in the surgery group is lower than the two other groups.</p>
Lattimer, 2013, ¹⁷ United Kingdom	<p>Clear description of subjects, outcomes, interventions, findings, actual <i>P</i> values.</p> <p>Measurement of reflux by ultrasound deemed to be accurate. Detailed</p>	<p>Study subjects and people measuring study outcomes were not blinded.</p> <p>EVLT group had more mild cases (C2), not taken into account for</p>

	<p>description of different venous outcomes.</p> <p>Sample size calculation.</p>	<p>analysis.</p> <p>No mention of losses to follow-up (number, reasons, analysis).</p> <p>Source population and hospital settings are unclear.</p> <p>Randomization was disclosed in a previous publication.</p>
<p>Samuel, 2013,²⁰ United Kingdom</p>	<p>Clear description of subjects, randomization procedure, outcomes, interventions, findings, actual <i>P</i> values.</p> <p>Measurement of reflux by duplex ultrasound deemed to be accurate.</p> <p>Sample size calculation for main outcome.</p>	<p>Study subjects and people measuring study outcomes were not blinded.</p> <p>Patients lost to follow-up not described.</p>
<p>CPGs</p>		
<p>Pavlovic, 2014,²³ International</p>	<p>Recommendations were well described.</p> <p>Recommendations were graded depending of strength of available evidence. Studies were cited.</p> <p>Patient preferences and side-effects have been considered.</p> <p>Authors declared no conflict of interest.</p>	<p>Methodology, health questions covered, composition of the development group, target users were poorly described.</p> <p>Assessment of bias in the covered literature has not been mentioned.</p> <p>Applicability has not been addressed.</p> <p>Not externally reviewed.</p> <p>No mention of an updating process.</p>
<p>NICE clinical guideline 168 [CG168]. Varicose veins in the legs: the diagnosis and management of varicose veins. July 2013,²² United Kingdom</p>	<ul style="list-style-type: none"> Review, development (clinical and economic): Very detailed CPG. <p>Clear description of scope, purpose, rigorous methodology, stakeholder involvement, evidences, safety issues, critical appraisal, recommendations, cost-effectiveness, tools for implementation.</p> <p>Conflicts of interests have been addressed.</p> <ul style="list-style-type: none"> Economic model: 	<ul style="list-style-type: none"> Review, development (clinical) Not clear on who provided external review. Economic model; Applicability of costs from United Kingdom to Canada remains uncertain.

	<p>Study had a well defined question, description of the competing treatments and established effectiveness of the therapies.</p> <p>Perspective, time horizon, discounting were stated.</p> <p>Costs with their references were disclosed and appropriate.</p> <p>Sensitivity analyses were performed and conclusions were deemed adequate.</p>	
<p>Rochon, 2012,²¹ USA (ACR Appropriateness Criteria® radiologic management of lower-extremity venous insufficiency)</p>	<p>Evidence was clearly presented, with their limitations.</p> <p>Key recommendations and treatment options were easily identifiable.</p>	<p>Health questions and objectives are not clearly defined.</p> <p>Methodology was described in a different document and was not specific to this guideline. Rigor of development couldn't be appraised.</p> <p>Composition of the development group was not mentioned.</p> <p>Reviewing process in not clear.</p> <p>Applicability and conflicts of interests were not addressed.</p>
<p>Recommendations</p>		
<p>Ontario Health Advisory Committee, 2013,²⁴ Canada</p>	<p>Recommendations based on previous HTAs providing evidence on EVLT and RFA.</p>	<p>No update of literature or evidence.</p>

ACR = American College of Radiology; C2 = C2 score on a CEAP (Clinical-Etiology-Anatomy-Pathophysiology) scale; CPG = clinical practice guidelines; EVLT = endovenous laser therapy; HTA = health technology assessment; MA = meta-analysis; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; *P* = probability value; RCT = randomized controlled trial; RFA = radio frequency ablation; SR = systematic review; USA = United States of America.

APPENDIX 4: Summary of Study Findings

First Author, Publication Year, Country	Main Study Findings	Authors' Conclusions
Health Technology Assessment		
Carroll, 2013, ¹⁴ United Kingdom	<ul style="list-style-type: none"> • 34 RCTs comprising 3,873 patients (range: 28 to 710 patients/trial) with VV; mean age range of 33 to 54 years; predominantly female (54 to 95%, depending on trial); majority of patients were C2 on CEAP score. 14 trials evaluated EVLT (8 vs surgery, 6 vs RFA, 1 vs UGFS); 13 trials evaluated RFA (6 vs surgery, 6 vs EVLT, 1 vs UGFS); 13 trials evaluated UGFS (10 vs surgery, 1 vs EVLT, 1 vs RFA) • <i>Clinical effectiveness and safety:</i> <ul style="list-style-type: none"> ○ <i>Failure of procedure:</i> EVLT: 5/467 (1%); RFA: 16/431 (4%); UGFS: 21/295 (7%); HLS: 20/681 (3%) ○ <i>Risk of technical recurrence [HR (95% CrI)]:</i> <ul style="list-style-type: none"> ▪ <i>EVLT vs stripping:</i> 6 mo: 0.70 (0.27 to 1.45); 1 y: 0.77 (0.37 to 1.54); 2 y: 0.84 (0.44 to 1.81) ▪ <i>RFA vs stripping:</i> 6 mo: 0.92 (0.39 to 2.11); 1 y: 0.93 (0.42 to 2.22); 2 y: 0.94 (0.42 to 2.51) ▪ <i>UGFS vs stripping:</i> 6 mo: 1.12 (0.53 to 2.27); 1 y: 1.02 (0.49 to 1.84); 2 y: 0.92 (0.43 to 1.60) ○ <i>Symptomatic recurrence:</i> Small number of reported events; no difference between groups ○ <i>VCSS:</i> UGFS vs stripping: -1.63 (-2.90 to -0.42), no difference between other groups. ○ <i>Time to return to work/normal activity:</i> 5 out of 7 studies favored RFA or UGFS vs surgery. ○ <i>Pain:</i> EVLT vs stripping: No difference between groups; RFA vs stripping: RFA favored 	<p>“This assessment of the currently available evidence suggests that there is little to choose between the minimally invasive techniques in terms of efficacy, and each offers a viable, clinical alternative to stripping. Based on data reviewed, only foam sclerotherapy offers a cost-effective alternative to stripping. Training and experience in the minimally invasive techniques might be required before more substantial, relative clinical benefits are apparent.” (p. 69)</p>

	<p>(median: -1.26 (95% CrI, -1.95 to -0.61); UGFS vs stripping: no difference.</p> <ul style="list-style-type: none"> ○ <i>Post-operative complications:</i> Hematoma, paresthesia, infection, phlebitis were commonly reported, but overall event numbers were small. DVT and PE were rare. ● <i>Cost-effectiveness:</i> <ul style="list-style-type: none"> ○ From SR: 4 economic studies identified (2 prospective analyses, 2 modeling analyses) <ul style="list-style-type: none"> ▪ Expected net benefits from different treatment approaches were similar, but sensitive to assumptions, creating uncertainty about relative CE. ○ From economic model: <ul style="list-style-type: none"> ▪ EVLT and RFA were more costly, while UGFS was less costly, than surgery with little difference in QALYs. ▪ Neither EVLT nor RFA were considered cost-effective compared with surgery at a threshold of £20,000 to £30,000. Robust model. ▪ UGFS was the most cost-effective with a probability of 90% at a threshold of £20,000-£50,000. Sensitive to time horizon. ▪ Between-treatment cost differentials were expected to vary by setting and time. 	
Systematic reviews		
<p>Nesbitt, 2014,¹⁵ United Kingdom</p>	<ul style="list-style-type: none"> ● UGFS vs surgery: <ul style="list-style-type: none"> ○ Clinician noted recurrence: no difference, (OR 1.74, CI 0.97 to 3.12, <i>P</i>=0.06) ○ Symptomatic recurrence: no difference, (OR 1.28, CI 0.66 to 	<p>“Currently available clinical trial evidence suggests that UGFS, EVLT and RFA are at least as effective as surgery in the treatment of great saphenous varicose veins. Due to large incompatibilities between</p>

	<p>2.49)</p> <ul style="list-style-type: none"> ○ Recanalisation (single study): < 4 months: OR 0.66 (CI 0.20 to 2.12) > 4 months: OR 5.05 (CI 1.67 to 15.28). ○ Neovascularisation (single study): OR 0.05 (CI 0.00 to 0.94). ○ Technical failure: no difference, OR 0.44 (CI 0.12 to 1.57). ● EVLT vs surgery; <ul style="list-style-type: none"> ○ Clinician noted recurrence: no difference, OR 0.72 (CI 0.43 to 1.22). ○ Symptomatic recurrence: no difference, OR 0.87 (CI 0.47 to 1.62). ○ Recanalisation: no difference, early: OR 1.05 (CI 0.09 to 12.77), late: OR 4.14 (CI 0.76 to 22.65, $P = 0.10$). ○ Neovascularization: reduced in EVLT with OR 0.05 (CI 0.01 to 0.22, $P < 0.0001$). ○ Technical failure: reduced in EVLT with OR 0.29 (CI 0.14 to 0.60, $P = 0.0009$). ○ Long-term (5 years) outcomes: (single study) similar findings between interventions. ● RFA vs surgery: <ul style="list-style-type: none"> ○ Clinician noted recurrence: no difference, OR 0.82 (CI 0.49 to 1.39). ○ Symptomatic recurrence (single study): no difference, OR 2.00 (CI 0.30 to 13.26) ○ Recanalisation: no difference, early: OR 0.68 (CI 0.01 to 81.18), late: OR 1.09 (CI 0.39 to 3.04). ○ Neovascularisation: no difference, OR 0.31 (CI 0.06 to 1.65). ○ Technical failure: no difference, OR 0.82 (CI 0.07 to 10.10). ● QoL scores, complications and pain: similar between groups. 	<p>trials and different time point measurements for outcomes, the evidence is lacking in robustness. Further randomised trials are needed, which should aim to report and analyse results in a congruent manner to facilitate future meta-analysis.” (p. 4)</p>
<p>Tellings, 2011,¹⁶ Netherlands</p>	<ul style="list-style-type: none"> ● 17 studies (RCT, non-RCT) in SSV VV including 10 EVLT, 5 surgery (stripping and/or ligation) and 2 UGFS studies. 	<p>“...lack of [published evidence]... specifically on the treatment of SSV insufficiency... (p. 183)</p>

	<p>EVLT studies comprised a range of 37 to 390 legs and follow-up of 0.5 month to 3 years. Surgery studies included 52 to 204 legs with follow-up of 1.5 months to 5 years. UGFS studies included 23 and 141 legs and follow-up of 1.5 months and 11 months.</p> <ul style="list-style-type: none"> ○ <i>Success rates:</i> Surgery ranged from 24% to 100%; EVLT ranged from 91% to 100%; UGFS ranged from 82% to 100%. Difference in success rate between surgery (47.8%) and EVLT/UGFS (94.9%), $P < 0.05$. ○ <i>Major complications:</i> Surgery: DVT (1.8% to 3.5%), sural nerve damage (2.1%); EVLT: DVT (1.3% to 5.7%); UGFS: none ○ <i>Paresthesia:</i> Surgery: 1.7% to 34%; EVLT: 1.3% to 11% 	<p>“...the results in the articles published do not allow us to draw definite conclusions on the ideal treatment for SSV insufficiency.” (p.183)</p>
RCTs		
<p>Mozafar, 2014,¹⁹ Iran</p>	<ul style="list-style-type: none"> ● 65 patients (EVLT: 30; HLS: 35) with GSV VV; mean age: 39 years; majority female (72%); 78% were C2 or C3 on CEAP score. ● After 12 months: <ul style="list-style-type: none"> ○ <i>Recurrence rate:</i> EVLT: 6.7%; HLS: 11.7% ○ <i>AVVSS score:</i> Lower in EVLT group ($P = 0.019$) ● After 18 months: <ul style="list-style-type: none"> ○ <i>AVVQ score:</i> Lower in EVLT group ($P = 0.008$) ○ <i>CEAP score:</i> Similar improvements in both groups after 1 week and sustained to 18 months. ○ No DVT reported in either group ○ Similar frequency of dysesthesia between groups (EVLT: 8.6%; HLS: 6.7%) ● Patient satisfaction was similar in both groups. 	<p>“The results of our study further establish the efficacy of EVLT as an alternative to conventional treatment and expand these findings to a broader population base to include people of Middle Eastern decent.” (p.770)</p>
<p>Biemans, 2013,¹⁸ Netherlands</p>	<ul style="list-style-type: none"> ● 223 patients/240 legs with primary incompetent GSV (EVLT: 80 legs, surgery: 80 legs); 82.3% were C2 or C3 on CEAP score; phlebectomies were 	<p>Results at 1-year demonstrate similar short-term efficacy and safety results for EVLT and conventional surgery. (p.733)</p>

	<p>permitted as an additional, initial treatment and again at 3 months.</p> <ul style="list-style-type: none"> • After 1 year follow-up: <ul style="list-style-type: none"> ○ <i>Anatomic success</i>: No difference between EVLT (88.5%) and surgery (88.2%); 10% of surgery patients had U/S-detected neovascularization of groin. ○ <i>Clinical improvement</i>: 47.6% of all patients improved by ≥ 2 categories in CEAP score with no between-group differences. ○ <i>Complications</i>: AE frequency was low (11 surgery pts vs 7 EVLT pts reported AEs) and not different between groups; no VTE was reported in any group. ○ <i>QoL</i>: No difference between groups, but 17 pts with bilateral GSV insufficiency excluded from analysis. 	
<p>Lattimer, 2013,¹⁷ United Kingdom</p>	<ul style="list-style-type: none"> • After 15 months: <ul style="list-style-type: none"> ○ Occlusion of GSV: EVLT 42/44 (95.5%) more effective vs UGFS 31/46 (67.4%). ○ Abolishment of global reflux: both equally effective. ○ Number of legs (n = 100, EVLT vs UGFS) with: total reflux abolition (18 vs 20), above-knee (6 vs 8), below-knee (12 vs 11), combined reflux (8 vs 7), loss to follow-up (6 vs 4). ○ Statistical reduction of VCSS, AVVQ and STS ($P < 0.0005$). No difference between groups. • Overall need for adjuvant therapy (sclerotherapy): 4.7 more frequent in the UGFS group vs EVLT group (47 vs 10). 	<p>“EVLA and UGFS are equally effective at abolishing global venous reflux with overall success of 41% and 43%, respectively. The high reflux rate was not related to deterioration in quality of life indicating that this reflux was largely asymptomatic.” (p. 394)</p>
<p>Samuel, 2013,²⁰ United Kingdom</p>	<ul style="list-style-type: none"> • 106 patients/legs (EVLT: 53; surgery: 53) with SSV VV; mean age: 48 years; majority female (70%); 81% were C2 on CEAP score. • Pain and return to normal functioning: <ul style="list-style-type: none"> ○ Pain scores lower ($P < 0.05$) in the EVLT group vs surgery group from day 4 to day 7. 	<p>“The immediate postoperative benefits and short-term technical outcomes of EVLT would support the future consideration of this procedure as the standard treatment of small saphenous insufficiency, provided the long-term results are no worse than following surgery.” (p. 425)</p>

	<ul style="list-style-type: none"> ○ Patients returned to normal functioning more quickly after EVLT than surgery ($P < 0.001$). ● After 6 weeks: <ul style="list-style-type: none"> ○ Abolition of SSV reflux: EVLT favored over surgery (96.2% vs 71.7%, $P < 0.001$) <ul style="list-style-type: none"> ▪ RR of early success with EVLT vs surgery: 1.34 (95% CI, 1.11 to 1.44); RD: 0.24 (95% CI, 0.09 to 0.30) ▪ NNT with EVLT to avoid one residual SSV post-procedure: 4.0 (95% CI, 3.2 to 10.9) ○ Sensory disturbance (especially sural nerve): More frequent with surgery than EVLT (26.4% vs 7.5%, $P = 0.009$) Most cases resolved after 1 year ($P = 0.434$). ○ Low frequency (EVLT vs surgery) of phlebitis (5.7% vs 1.9%), infection (0 vs 1.9%), hematoma (0 vs 3.8%), DVT (0 vs 1.9%). ● After 1 year: <ul style="list-style-type: none"> ○ Clinical recurrence: Similar in surgery vs EVLT (16.9% vs 9.4%, $P = 0.390$) ○ VCSS: Similar improvement between groups. ○ QoL: <ul style="list-style-type: none"> ▪ AVVQ: Similar improvement between groups. ▪ SF-36 V1, EQ-5D: Similar improvement between groups. 	
Clinical practice guidelines		
Pavlovic, 2014, ²³ International	<ul style="list-style-type: none"> ● Only clinical evidence considered; no health economic guidance issued. ● Veins indicated for EVTA (all GRADE I recommendations): <ul style="list-style-type: none"> ○ GSV ○ SSV ○ Accessory SV (intrafascial part) ○ Giacomini vein and cranial 	

	<ul style="list-style-type: none"> ○ extension of SSV ○ Other superficial veins in subcutaneous tissue ○ Insufficient perforating veins ○ Residual intrafascial veins post-treatment ○ Venous malformations ● While RFA has some specific requirements for vein segment length, EVLT does not. ● To enable catheter advancement, EVTA requires that veins be free of synechiae or membrane webs or tortuosity. ● Calculations are recommended for determining the appropriate energy for treatment by EVTA (GRADE IA). <ul style="list-style-type: none"> ○ RFA: energy delivery will vary by system employed (e.g., Closure FAST™, Celon™ system). ○ EVLT: Appropriate energy density is the main driver of success. ● Major complications to consider in EVTA (GRADE IC): <ul style="list-style-type: none"> ○ DVT/PE (though reported post-procedure incidence low: 0-2%) ○ Damage to arteries (e.g., arterial fistulas – very rare) ○ Severe nerve damage (very rare) ○ Skin burns (especially when treated without tumescence) ○ Infection ○ Intra-procedural fiber breakage ○ Stroke (based on single case report) ● Minor complications to consider in EVTA (GRADE IC):: <ul style="list-style-type: none"> ○ Pain ○ Bruising ○ Erythema ○ Hematoma ○ Hyperpigmentation ○ Paresthesias ○ Tender or non-tender palpable treated vessel (especially thigh GSV) 	
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	<ul style="list-style-type: none"> ○ Infection ○ Telangiectatic matting ● EVTA is often performed with adjunctive phlebectomy or UGFS. ● During one procedure, EVTA may be carried out on ≥ 2 incompetent veins. 	
<p>NICE clinical guideline 168 [CG168]. Varicose veins in the legs: the diagnosis and management of varicose veins. July 2013,²² UK</p>	<ul style="list-style-type: none"> ● As interventions for VV and truncal reflux, the following treatment hierarchy is recommended: <ul style="list-style-type: none"> ○ RFA > EVLT > UGFS > surgery ○ Compression hosiery should only be considered as a treatment option if interventional therapy is not indicated. ● Pregnant women with VV should generally receive compression hosiery for symptomatic relief instead of interventional treatment. ● Key research gaps: <ul style="list-style-type: none"> ○ Natural history of VV not established ○ Evidence gap in clinical and cost effectiveness of compression hosiery ○ Evidence gap in clinical and cost effectiveness of adjunctive tributary treatment during EVTA ○ Disease severity/different stages of disease: higher CEAP scores do not necessarily correlate with higher VV severity; detecting changes in QoL may be confounded by differences in symptom perception; no method to express severity quantitatively in terms of degree of venous reflux in superficial venous system ● Cost-effectiveness: systematic review + economic modeling. <ul style="list-style-type: none"> ○ UGFS is the least costly (£718) and surgery is the most costly (£1,222) treatment. ○ EVTA have an ICER of £3,161/QALY compared with UGFS. ○ EVTA has a 71% probability of being the most cost-effective vs 	

	<p>23% for UGFS.</p> <ul style="list-style-type: none"> ○ Results are robust in sensitivity analyses. 	
<p>Rochon, 2012,²¹ USA (ACR Appropriateness Criteria® radiologic management of lower-extremity venous insufficiency)</p>	<ul style="list-style-type: none"> ● EVLT or RFA are rated as ‘usually appropriate’ (i.e., score of 7 to 9 on scale of 1 to 9) in the following clinical situations: <ul style="list-style-type: none"> ○ Asymptomatic bilateral GSV insufficiency with visible VV. Patient desires treatment for cosmesis. ○ Left SSV insufficiency resulting in intermittent pain and swelling without skin discoloration or ulceration. ○ Left GSV insufficiency with associated lower leg skin ulceration. ○ Symptomatic bilateral GSV insufficiency with remote history of DVT with no residual thrombus present. ○ Right GSV insufficiency s/p vein stripping 1 year ago with persistent lower-extremity swelling. Reflux is noted in the below-knee GSV measuring ≤ 5 mm. ● No economic guidance issued. 	
<p>Ontario Health Advisory Committee, 2013,²⁴ Canada</p>	<ul style="list-style-type: none"> ● EVLT and RFA are less invasive, safe and cost-effective alternatives to surgery for treatment of symptomatic VV with saphenous reflux. ● Should be made available when bleeding, thrombophlebitis, venous ulcer. Chronic venous reflux also included if based on severity scale like VCSS. ● Cosmetic intervention should not be publicly funded. ● Quality assurance mechanism should be implemented. 	

ACR = American College of radiology; AE = adverse event; AVVQ = Aberdeen Varicose Vein Questionnaire; C2, C3 = score of 2 or 3 on CEAP instrument; CE = cost-effectiveness; CEAP = clinical status, etiology, anatomy, pathophysiology scale; CI = confidence interval; CrI = credible interval; DVT = deep vein thrombosis; EVLT = endovenous laser therapy; EQ-5D = EuroQol 5D; EVTA = endovenous thermal ablation (includes EVLT and RFA); GSV = great saphenous vein; HLS = high ligation and stripping; HR = hazard ratio; ICER = Incremental cost-effectiveness ratio; mo = month; NNT = number needed to treat; P = probability value; PE = pulmonary embolism; pts = patients; QALY = quality-adjusted life year; QoL = quality of life; RCT = randomized controlled trial; RD = risk difference; RFA = radiofrequency ablation; RR = relative risk; SF-36 V1 = Short-Form Health Survey (UK version); s/p = status post; SR = systematic review; SSV = small saphenous vein; STS = saphenous treatment score; SV =

saphenous veins; UGFS = ultrasound-guided foam sclerotherapy; U/S = ultrasound; USA = United States of America; VCSS = Venous Clinical Severity Score; vs = versus; VTE = venous thromboembolism; VV = varicose veins; y = year.